SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Slo-Phyllin 250mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Slo-Phyllin 60mg capsules each contain theophylline (anhydrous) EP 60mg
Slo-Phyllin 125mg capsules each contain theophylline (anhydrous) EP 125mg
Slo-Phyllin 250mg capsules each contain theophylline (anhydrous) EP 250mg
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule.

Hard gelatin capsules with opaque purple body and clear colourless cap, printed radially in black with Slo-phyllin 250 on one half and Lipha on the other, and containing white-grey to light yellow pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As a bronchodilator in the symptomatic and prophylactic treatment of asthma and for reversible bronchoconstriction associated with chronic bronchitis and bronchial asthma.
Theophylline should not be used as first drug of choice in the treatment of asthma in children.

4.2 Posology and method of administration

<table>
<thead>
<tr>
<th>Method of administration</th>
<th>Oral</th>
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Dosage
Children:
Slo-Phyllin should not be used in children below 6 years of age. Other dosage forms are available that are more suitable for children aged less than 6 years.

over 12 years:  250-500 mg twice daily

Adults:  250-500 mg twice daily

Elderly:  There is a tendency for theophylline clearance to decrease with age leading to higher serum levels. A reduction of the adult dosage may therefore be necessary and close monitoring is advised.

Each patient should be titrated to a suitable dosage regimen by clinical assessment. It may also be necessary to measure plasma theophylline levels.

Initially the lowest dosage for each group is recommended. This may be increased gradually if optimal bronchodilator effects are not achieved. The total dosage should not normally exceed 24 mg/kg body weight for children and 13 mg/kg for adults. However the plasma theophylline level measured 4-8 hours after dosing and at least three days after any dosage adjustment, provides a more accurate assessment of the patients dosage need, especially as significant variations in the rate of drug elimination can occur between individuals. The following table provides a guide:

<table>
<thead>
<tr>
<th>Plasma level (mcg/ml)</th>
<th>Result</th>
<th>Directions (if clinically indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 5</td>
<td>Too low</td>
<td>Increase dose by 25%</td>
</tr>
<tr>
<td>5-12*</td>
<td>Correct</td>
<td>Maintain dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Plasma concentration of up to 20 mcg/ml can be necessary in some cases</td>
</tr>
<tr>
<td>20-25</td>
<td>Too high</td>
<td>Decrease dose by 10%</td>
</tr>
<tr>
<td>25-30</td>
<td>Too high</td>
<td>Miss next dose and decrease subsequent doses by 25%</td>
</tr>
<tr>
<td>Over 30</td>
<td>Too high</td>
<td>Miss next two doses and decrease subsequent doses by 50%</td>
</tr>
</tbody>
</table>

It is advisable to recheck the plasma level after dose adjustment and every 6-12 months.

It is not possible to ensure bioequivalence between different prolonged release theophylline products. Once titrated to an effective dose, patients should not be changed from Slo-Phyllin to another prolonged release xanthine preparation without re-titration and clinical assessment.

4.3 Contraindications

Hypersensitivity to theophylline or other xanthines, or hypersensitivity to any of the excipients listed in section 6.1.
Concomitant use of theophylline and ephedrine in children.

Children under 6 months of age.

Recent myocardial infarction

Acute tachycardia

4.4 Special warnings and precautions for use

Smoking and alcohol consumption can increase the clearance of theophylline and a higher dose may be necessary.

Careful monitoring is recommended for patients with congestive heart failure, chronic alcoholism, hepatic dysfunction, or viral infections, as they may have a lower clearance of theophylline, which could lead to higher than normal plasma levels.

Caution should be exercised in patients with peptic ulcers, cardiac arrhythmias, other cardiovascular diseases, hyperthyroidism or hypertension.

Slo-Phyllin should not be used concurrently with other preparations containing xanthines derivatives. If it is necessary to administer aminophylline to a patient who is already receiving Slo-Phyllin, plasma theophylline concentration should be monitored.

The use of alternative treatments is advised in patients with a history of seizures, as these may be exacerbated by theophylline.

Special caution is required in patients receiving electroconvulsive therapy, as theophylline can prolong seizures. Status epilepticus may occur.

Slo-Phyllin should only be used if highly necessary and with caution in patients with porphyria or severe kidney function disorders.

Use of Slo-Phyllin in elderly patients, those with multiple morbidity, severe diseases and/or those receiving intensive medicinal treatment is associated with increased risk of intoxication. These patients should therefore be monitored using therapeutic drug monitoring (TDM) (see also section 4.2).

In case of insufficient effect of the recommended dose and in case of adverse events, theophylline plasma concentration should be monitored.

This product contains small quantities of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Acute febrile illness

Fever decreases the clearance of theophylline. It may be necessary to decrease the dose to avoid intoxication.
4.5 Interaction with other medicinal products and other forms of interaction

Theophylline has been reported to interact with a number of drugs. Due to the many interactions of theophylline, monitoring of serum theophylline concentrations is recommended during long-term use of Slo-Phyllin with other medicinal products. This also applies after discontinuation.

Theophylline has synergy with other medicinal products that contain xanthine, beta-sympathomimetics, caffeine and similar substances. Coffee increases the effect of theophylline.

The following increase clearance and it may therefore be necessary to increase dosage to ensure therapeutic effect: barbiturates, carbamazepine, lithium, phenytoin, rifampicin, primidone, ritonavir, aminoglutethimide and sulphinpyrazone.

The following reduce clearance and a reduced dosage may therefore be necessary to avoid side-effects: allopurinol, cimetidine, corticosteroids, diltiazem, macrolide antibiotics (e.g., erythromycin), frusemide, isoprenaline, oral contraceptives, thiaobendazole, quinolones, isonicotinic acid hydrazide, propranolol, propafenone, mexiletine, ticlopidine, alpha-interferon, rofecoxib, pentoxifylline, fluvoxamine, viloxazine, disulfiram, zileuton, phenylpropanolamine, BCG vaccine and verapamil. The theophylline dose should be reduced to a maximum of 60% during concomitant treatment with ciprofloxacin, to a maximum of 30% with enoxacin, and to 50% of the recommended dose with grepafloxacin or clinafloxacin. Other quinolones (e.g. pefloxacin, pipemidic acid) can also increase the effect of theophylline medicinal products. Close monitoring of theophylline concentrations is therefore strongly recommended during concomitant treatment with quinolones.

Theophylline levels can rise or fall during concomitant use with isoniazid. Monitoring of theophylline levels is indicated.

The effect of lithium, beta receptor blockers, adenosine and benzodiazepines (e.g. diazepam) can be reduced during concomitant administration of theophylline.

Theophylline increases the diuretic effect of diuretics.

There is evidence that the seizure threshold of the brain can be reduced during concomitant administration of certain fluoroquinolones or imipenem.

Administration of halothane can cause severe heart rhythm disturbances in patients receiving theophylline.

There is some evidence of an interaction between theophylline and influenza vaccine.

Individual cases of theophylline overdose symptoms have been also been reported following concomitant treatment with ranitidine, acyclovir or zafirlukast.

Xanthines can potentiate hypokalaemia resulting from beta2 agonist therapy, steroids, diuretics and hypoxia. Particular caution is advised in severe asthma. It is recommended that serum potassium levels are monitored in such situations.
The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their theophylline dose halved and plasma theophylline should be monitored closely.

Plasma concentrations of theophylline can be reduced by concomitant use of the herbal remedy St John’s wort (Hypericum perforatum).

4.6 Fertility, pregnancy and lactation

There is not enough experience concerning use of theophylline during the first trimester of pregnancy. Administration of Slo-Phyllin should therefore be avoided during this period.

During the second and third trimesters, theophylline should only be used if the benefit/risk assessment is compelling, as it crosses the placental barrier and can have sympathomimetic effects in the foetus.

Plasma protein binding as well as clearance of theophylline can decrease as pregnancy progresses. Dose reduction may therefore be necessary to avoid adverse effects. If a patient is treated with theophylline at the end of pregnancy, it can inhibit contractions. Newborns exposed prenatally must be monitored carefully for the effects of theophylline.

Theophylline is excreted in breast milk and therapeutic serum concentrations can be reached in children. For this reason, the therapeutic theophylline dose should be kept as low as possible in breast-feeding patients. Breast-feeding should preferably take place immediately before administration of the medicinal product.

The breast-fed infant must be carefully monitored for any effects of theophylline. If higher therapeutic doses are required, it must be discontinued.

4.7 Effects on ability to drive and use machines

This medicinal product can affect the ability to react, even when used as intended. The ability to drive, use machines or work at great heights or without sure footing can therefore be impaired. This applies to a greater extent when the drug is combined with alcohol or medicinal products that can impair the ability to react.

4.8 Undesirable effects

Metabolism, electrolytes
Changes in serum electrolytes, particularly hypokalemia, increases in serum calcium and creatinine levels, hyperglycemia and hyperuricemia. Diuresis (especially in children).

Immune system
Hypersensitivity reactions to theophylline (such as rash, pruritus, urticaria, bronchospasm) including anaphylactic reactions.

**Nervous system**
Headache, agitation, tremor, restlessness, insomnia, dizziness, convulsions. CNS stimulation (especially in children).

**Cardiovascular system**
Tachycardia, arrhythmia, palpitations, drop in blood pressure.

**Gastrointestinal tract**
Gastrointestinal disorders, nausea, vomiting, stimulation of gastric acid secretion. Due to a reduction in lower esophageal sphincter tone, existing gastroesophageal reflux at night can be increased.

**Urogenital tract**
Increased urine output.

More severe adverse effects can occur in cases of individual hypersensitivity or overdose (blood theophylline levels above 20 µg/ml) (see Section 4.9).

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

### 4.9 Overdose

**Symptoms of intoxication**
When serum theophylline levels are between 20 and 25 µg/ml, the known adverse effects of theophylline are generally observed with greater intensity (see Section 4.8). Toxic effects such as seizures, a sudden drop in blood pressure, ventricular arrhythmia, cardiovascular collapse, rhabdomyolysis and severe gastrointestinal symptoms (such as gastrointestinal bleeding) can occur mainly when serum theophylline levels are higher than 25 µg/ml. These reactions can also occur without the precursors of milder adverse effects. Children in particular can have sensitivity reactions to theophylline overdose. When overdose is caused by prolonged-release theophylline preparations, the onset of symptoms can be delayed.
In patients with high individual sensitivity to theophylline, severe symptoms of overdose are possible with serum concentrations lower than those mentioned above.

**Treatment of overdose**
*In patients with mild symptoms of overdose:* The preparation in question should be discontinued and serum theophylline levels assayed. If treatment is resumed, the dose in question should be reduced.
Treatment of all theophylline overdoses

Gastric lavage can be considered for up to 2 hours after oral administration. For further removal of theophylline as well as after overdose with intravenously-administered theophylline, activated charcoal should be administered repeatedly, if necessary in combination with a fast-acting laxative (e.g. sodium sulfate).

In patients with central nervous system reactions (e.g. restlessness and seizures): IV diazepam, 0.1-0.3 mg/kg body weight, up to 15 mg.

In life-threatening cases:

- Monitoring of vital functions,
- Airways kept open (intubation),
- Supply of oxygen,
- if necessary, IV volume replacement with plasma expanders,
- monitoring and possible correction of water and electrolyte balance,
- Hemoperfusion (see below).

In patients with life-threatening heart rhythm disturbances:
IV administration of propranolol in non-asthmatic patients (1 mg in adults, 0.02 mg/kg body weight in children): this dose can be repeated every 5 to 10 minutes until heart rhythm normalizes or up to the maximum dose of 0.1 mg/kg body weight.

Warning:
Propranolol can trigger severe bronchospasm in asthmatic patients. Verapamil should therefore be used in asthmatic patients.
In particularly severe cases of overdose where response to the measures listed above is insufficient, as well as in patients with very high serum theophylline levels, rapid and complete removal of the drug can be achieved with hemoperfusion or hemodialysis. However, this is generally not necessary, as theophylline is metabolized relatively quickly.

Further treatment of Slo-Phyllin overdose is based on the extent and course of the intoxication as well as existing symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
The mechanism of action of theophylline is unclear although a number of pharmacological actions have been implicated. The principal of these are:-

1) Inhibition of the enzyme phosphodiesterase leading to raised cyclic AMP
levels.

2) Antagonism of adenosine receptors.

3) Inhibition of the intracellular release of calcium.

4) Stimulation of catecholamine release.

5) Anti-inflammatory action possible involving the inhibition of submucosal action.

5.2 Pharmacokinetic properties

Following administration of Slo-Phyllin capsules at an appropriate twice-daily dosage, peak levels occur 4-8 hours after dosing, and steady state is achieved in three days. Effective plasma concentrations: 5 – 12 µg/ml (do not exceed 20 µg/ml). Theophylline is mainly excreted by the kidneys.

5.3 Preclinical safety data

No adverse effects can be predicted from animal toxicology studies other than those documented from human use of theophylline.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients are sucrose, maize starch, refined bleached shellac, talc and gelatin. Capsule shell colours - erythrosine (E127), indigo carmine (E132) and titanium dioxide (E171). Printing ink: black iron oxide (E172), shellac glaze, propylene glycol.

6.2 Incompatibilities
6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container

PVC/Foil blister packs of 56 tablets
Sample PVC/Foil blister packs of 8 tablets
Plastic container of 100 tablets.

6.6 Special precautions for disposal

Patients should be instructed not to chew or suck the capsules or pellets as this destroys the prolonged release properties. However, for those who experience difficulty in swallowing capsules, the contents of a capsule may be sprinkled on to a spoonful of soft food, e.g. yoghurt.

7 MARKETING AUTHORISATION HOLDER

Merck Serono Ltd
Bedfont Cross, Stanwell Road
Feltham, Middlesex,
TW14 8NX, UK

8 MARKETING AUTHORISATION NUMBER(S)
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date granted – 11/01/77
Last UK Renewal - 27.01.97

10 DATE OF REVISION OF THE TEXT

26/07/2016